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(71)(72) Applicant and Inventor: HARRIS, Stephen, J. [GB/IE]; 10 Broadford Crescent, Ballinteer, Dublin 16 (IE).

(74) Agents: GATES, Marie, Christina, Esther et al.; Tomkins & Co., 5 Dartmouth Road, Dublin 6 (IE).

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(54) Title: CALIXARENE-BASED COMPOUNDS HAVING ANTIBACTERIAL, ANTIFUNGAL, ANTICANCER-HIV ACTIVITY

(57) Abstract

Calixarene-based compounds are described which have biological activity, particularly anti-bacterial, anti-fungal, anti-cancer and anti-viral activity. Some compounds have been found to have anti-HIV activity. The compounds are calixarenes or oxacalixarenes, acylic phenyl-formaldehyde oligomers, cyclotriveratrylene derivatives, cyclic tetrameric resorcinol-aldehyde derivatives known as Hogberg compounds and cyclic tetrameric pyrogallol-aldehyde derivatives.

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CALIXARENE-BASED COMPOUNDS HAVING ANTIBACTERIAL, ANTIFUNGAL, ANTICANCER HIV ACTIVITY

The present invention relates to compounds having biological activity, particularly calixarene-based compounds, having anti- bacterial, anti-fungal, anti-cancer and anti-viral, particularly anti-HIV activity.

The virus that causes AIDS, the human immunodeficiency virus HIV is believed to be one of the major threats to human life and health worldwide. Even back in 1988 an article in Scientific American by J. M. Mann, J. Chin, P. Piot and T. Quinn estimated that more than a quarter of a million AIDS cases had occurred up to then and that 5-10 million people were infected with HIV worldwide.

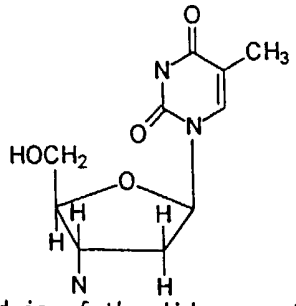
The HIV has been studied more intensively than any other virus and we now have a general picture of how the genes and proteins in the HIV virus particle operate, although we don't have a clear understanding of what controls the replication and how it destroys the human immune system. There are in fact many strains of HIV. The two main ones are HIV-1 and HIV-2. HIV-2 is prevalent in West Africa and produces a less severe disease than does HIV-1 the most common form elsewhere.

The life cycle of the virus is described below in some detail since for a drug to be effective it has to interfere with at least one stage of its life cycle. The HIV virus particle is roughly spherically shaped and is about a thousandth of a millimetre across. Its outer membrane consists of lipid molecules which possess many viral protein spikes projecting outwards. Each spike is thought to consist of four molecules of glycoprotein gp120 with the same number of glycoprotein gp41 molecules embedded in the membrane itself. These envelope proteins come into play when HIV binds and then enters target cells. Gp120 can bind tightly to CD4 proteins sited in the membranes of immune system cells especially T lymphocytes also called T cells. This is the first stage of the infection which is followed by fusion of the virus and T cell membrane, a process governed by the gp41 envelope protein. The result is that the contents of the virus core are thus freed to enter the cell. The virus core is surrounded by matrix protein called p17 and is itself in the shape of a hollow cone made of another protein p24 containing the genetic material of the virus.

Being a retrovirus this genetic material is in the form of RNA

(ribonucleic acid) consisting of two RNA strands. These are in turn attached to molecules of an enzyme, reverse transcriptase, which transcribes the viral RNA into DNA once virus has entered the cell. Coexisting with RNA are an integrase, a protease, a ribonuclease and other enzymes. Once in the cell the viral RNA is converted to DNA which then enters the cell nucleus. The next step is integration of viral DNA into host chromosomes. This is followed by cell proteins binding to DNA initiating transcription. Short RNA molecules then leave the nucleus and make viral regulatory proteins followed by medium length and long RNA which generate structural and enzymatic proteins. These assemble to form new viruses (replication-viral budding) (1).

The drug of choice in AIDS treatment up to this time has been Wellcome's Retrovir or Zidovudine which is 3'-Azido-2',3'- dideoxythymidine or AZT for short:



This compound is of the dideoxynucleoside type and blocks HIV replication by inhibiting reverse transcriptase. (Such compounds are actually modified in vivo in the target cell to active 5'-triphosphates (2). Other nucleoside drugs believed to work in a similar way are Didanosine ddI (or Videx) which has been developed by Bristol-Myers Squibb and dideoxycytidine ddC of Roche. 2',3'-Didehydro-2',3'- dideoxythymidine Stauvudine, D4T was developed by Bristol-Myers Squibb after ddI as a cheaper alternative to AZT (2,3).

However, the important point to be made here is that all these drugs are highly toxic, potentially nerve damaging materials. In addition AZT can give rise to anaemia although this undesirable side effect may be counteracted by co-administration of drugs such as erythropoietin. The least toxic alternative to AZT is Triton Bioscience's 3'-azido-dideoxy-uridine AzdU but being structurally similar to AZT may have similar resistance problems (3). Indeed apart from the toxic side effects associated with the use of AZT the virus quickly develops resistance to this drug (4). Researchers had hoped for several years that using a combination of these nucleoside inhibitors would provide benefits over individual drugs used alone. However, recent such results presented in Berlin were very disappointing. A large recent

controversial French and British Study of AZT indicates that its early use in HIV-infected individuals provided no survival benefits (5).

New non-nucleoside reverse transcriptase inhibitors which have selective anti HIV-1 activity are certain benzodiazepine analogs and thione derivatives developed by Pauwels and coworkers (2) but again resistance to these compounds develops very rapidly blunting their clinical usefulness.

Several new drugs have found to help block the step prior to that involving reverse transcriptase i.e. the transcription of RNA to double stranded DNA which is the step of entry, uncoating and RNA release. These are bicyclams and hypericin currently undergoing clinical trials (2). Another approach targetting the even earlier step, that of the binding of gp120 to CD4 has involved utilisation of soluble CD4 to flood the body and act as a decoy for the virus or attachment of CD4 to an antibody or antibody-toxin complex. However, again results have been very disappointing.

Low molecular weight dextran sulphate has been demonstrated to block the binding of the HIV virus particles to CD4 (its target cells) in in vitro testing. However, again clinical testing provided no benefits, probably related to the ease of degradation of this anionic polysaccharide (6).

A wide range of known and potential anti HIV-1 agents were tested for their in vitro anti HIV-1 activity (7). Apart from AZT the most active agent found was RO 31-8959 (XVII) a compound developed by N. A. Roberts and coworkers (8). This compound worked at a much later stage in the life cycle of the HIV virus namely as a HIV-1 protease inhibitor. In fact two protease inhibitors have now entered clinical trials (2).

More recent developments have involved the use of anti-sense oligodeoxynucleosides (short segments of DNA) that may hybridize to messenger RNA and inhibit translation. In any event they have been demonstrated to possess in vitro anti HIV activity (2).

A very late stage in the HIV life cycle which has been targetted is that of viral budding which has at least been partially blocked by use of interferon alpha.

Prem Mohan and coworkers of the University of Illinois, Chicago have

recently improved the anti HIV activity of naphthalene disulphonic acid derivatives to 6 μM for HIV inhibition (4) in in vitro testing. He believes they work by acting at the earliest stage of the HIV virus life cycle namely binding onto gp120 on the virus's surface. He believes that certain sites on the HIV's protein carry positive charges and that the negatively charged sulphonic acids can block these and prevent the virus entering its target cell. Mohan's coworker Sandeep Varma has recently found that these molecules also inhibit reverse transcriptase.

Another very recent development reported is utilisation of soluble fullerenes to inhibit the key viral enzyme HIV-protease competitively at 5 μM concentration by S. H. Friedman and coworkers at UCSF (9) in in vitro testing.

However, the levels at which these novel agents are effective is relatively high and little is known of their toxicity to healthy cells (cytoxicity).

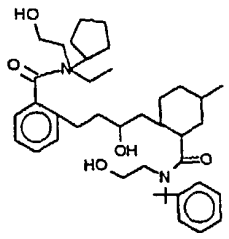
The concentration at which an HIV-1 drug is effective is designated EC_{50} which represents when the number of cells protected from HIV injection is half of the total. The antigen Agp120 assay - the virus related antigen - is related to the number of virus particles produced by measuring glycoprotein gp 120 in infected cell cultures uM (micromolar). Thus EC_{50} represents the concentration which reduces required Antigen gp 120 by 50% in infected cell cultures. The concentration of the drug which reduces cell growth by 50% is designated TC_{50} μM.

Of course the lower the EC_{50} concentration the better but the real criterion of effectiveness in in vitro testing on cell cultures is the Therapeutic index which is TC_{50}/EC_{50} ratio so as not to damage healthy cells. Thus AZT has an EC_{50} of Ca 0.016 μM with a TC_{50}>1000 uM. This results in a therapeutic index of >1000/0.016 = > 62,500. Of course human beings and animals are more than a collection of cells and in spite of the high Therapeutic Index, AZT is quite toxic, giving rise to nerve damage and anaemia among other things (3). Nevertheless such tests on cell cultures indicate what is a potential anti HIV drug.

Other factors relevant to the usefulness of an anti HIV drug are physical properties such as water-solubility for drug absorbtion by the patient and stability of the compound after oral intake. Thus the potentially useful

drug, the anionic polysaccharide, dextran sulphate is poorly absorbed orally and degrades after oral intake before entry into the plasma (6). Another important factor is ease of synthesis of the drug and hence drug cost which is relatively high for AZT and most other drugs produced to date which are potentially useful in combatting AIDS.

Very recently Agowan Pharmaceuticals, San Diego have developed orally active compounds that are potent inhibitors of a key enzyme of HIV namely HIV protease. The compound has been called AS-1284(10)



It is an object of the present invention to provide novel, and easily synthesised compounds having biological activity, particularly having improved anti-HIV activity.

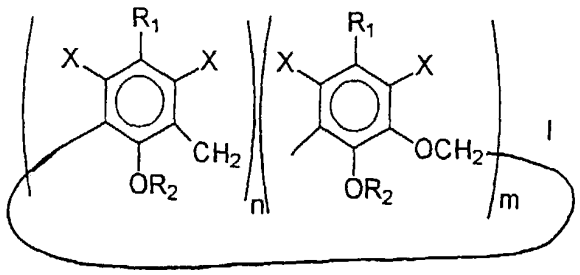
Such compounds are cyclic and acyclic phenol-aldehyde oligomers and their wide range of derivatives preferably carboxylic acid salt derivatives which renders them water soluble. These compounds have shown surprisingly good anti-HIV activity, particularly against HIV-1.

The first class of compounds are derived from cyclic phenol-formaldehyde calixarenes and oxacalixarenes.

Polyoxyethylene ethers of calixarenes have been shown to have biological and biochemical effects (Jain et al Biochem J. (1985), 227 p. 789-94). At least some of the derivatives of calixarenes/oxacalixarenes of the present invention possess metal ion complexing ability. A range of these already known to complex metal ions has been described:- US Patents 5,132,345; 4,556,700; 4,642,362; 4,866,198; 4,882,449; 4,699,966; 4,855,461; 4,908,399; 4,933,407; EP 237,265; 262,910 and 309,291.

The present invention provides calixarene or oxacalixarene derivatives of

the formula I



wherein n + m = 3 - 8

m = 0 - 3

n = 0 - 8

R^1 is H, halogen, hydrocarbyl, aryl, hydrocarbylaryl or a substituted derivative thereof, NO_2, SO_3M where M is an alkali metal, SO_3H, $R^1 = OR^2, R^2$ described below,

X is halogen, NO_2, CO_2H, CN or other electron withdrawing group.

$R^2 = CH_2\overset{O}{\overset{\|}{C}}OR^3$ or $CH_2\overset{O}{\overset{\|}{C}}\underset{P}{OM^P}$ or $CH_2\overset{O}{\overset{\|}{C}}N\begin{matrix}R^4\\R^5\end{matrix}$

R^3 is alkyl or a substituted derivative thereof,

M is a metal or ammonium ion, P is the charge on the metal ion, R^4 or R^5 may be the same or different, or both may be part of amino acid ester or poly(amino acid ester) of one or more of the same or different amino acids or part of a cyclic polyene antibiotic/antifungal drug or part of a cyclic nitrogen heterocycle,

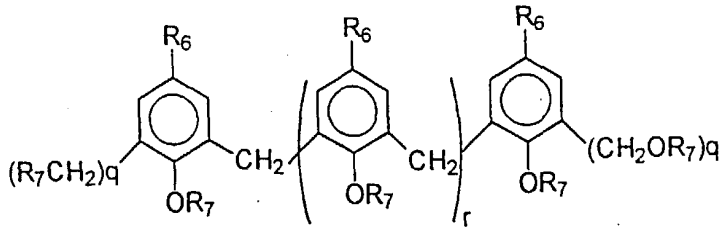
R^1 is preferably NO_2 or a halogen, particularly bromine , R^3 is preferably $CH_2CH_2OCH_3$ when R^1 is ethyl, n is 7 and m is 0, M is preferably an alkali metal or alkaline earth metal or ammonium or a substituted derivative thereof, R^2 is preferably CH_2CO_2K or $CH_2CO_2NH_4$.

The cyclic polyene drug may be Amphotericin B or a lactam antibiotic such as a penicillin derivative or the aminoglucoside sinefungin.

The cyclic nitrogen heterocycle may be an aminotetrazole or aminotriazole.

In a second aspect the invention provides open chain, i.e. acyclic

phenol-formaldehyde oligomers of formula II



II

wherein q = 0-1, r = 0-6; R^6 is alkyl, H, halogen, aryl, alkaryl or a substituted derivative thereof,

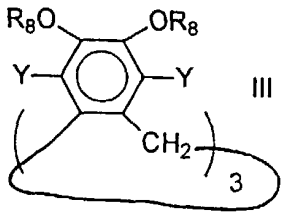
R^7 is H or $CH_2CO_2\underset{p}{M}^p$ where p is the charge on the metal ion,

M is a metal ion,

R^6 is preferably halogen. M is preferably an alkaline metal or alkaline earth metal. R^7 is preferably CH_2CO_2K.

Phenolic oligomers may be made by the procedure of B. Dhawan and C.D. Gutsche, J. Org. Chem 1983 48 p.1536, and the ester modified oligomers by the procedure of U.K. Pat. Appln. GB 2,200,124 A1 by S.J. Harris and B.J. Kneafsey assigned to Loctite (Ireland).

In a third aspect the invention provides cyclotriveratrylene derivatives of formula III



III

wherein Y is H, halogen, NO_2

R^8 is H or $CH_2CO_2R^9$ or $CH_2CO_2\underset{p}{M}^p$

R^9 is alkyl, aryl, alkaryl or a substituted derivative thereof,

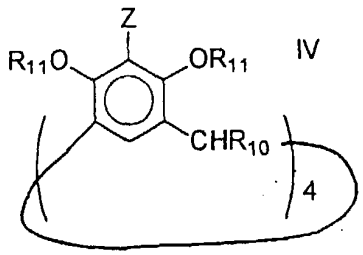
M is metal ion, and p is the charge on the metal ion.

Preferably Y is halogen and R^8 is CH_2CO_2K.

M is preferably an alkaline metal or alkaline earth metal.

The parent cyclotriveratrylene may be synthesised by the process of J.Org. Chem 43 (9) 1978 p.1808 by J.A. Hyatt.

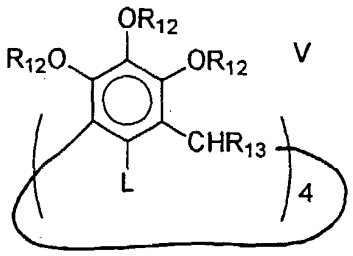
In a fourth aspect the invention provides cyclic tetrameric resorcinol-aldehyde derivatives known as Hogberg Compounds, (J.Org. Chem. 1980 45 p.4498 by A.G.S. Hogberg) of formula IV



IV

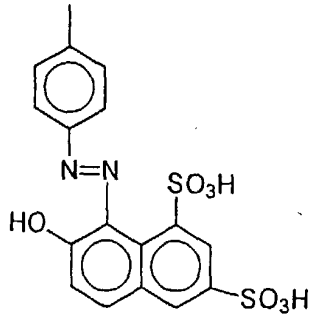
wherein R^{11} is the same as R^{8} defined above, Z is halogen or nitro, R^{10} is alkyl, aryl, alkaryl or a substituted derivative thereof. Preferably Z is halogen and R^{11} is CH_2CO_2K.

In a fifth aspect the invention provides cyclic tetrameric pyrogallol-aldehyde derivatives, (Eur. Pat. Appl. EP 400,773 5th Dec. 1990 by J. Holmes, P.Tasker of ICI) of formula V

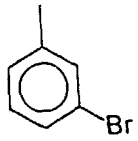


V

wherein R^{12} is the same as R^{8} defined above,
L is H, halogen or nitro, or other electron withdrawing group,
R^{13} is alkyl, aryl, alkaryl or a substituted derivative thereof or when R^{12}=H, L=H, R^{13}=



Preferably L is halogen e.g. Bromine, R^{12} is $CH_2CO_2NH_4$, CH_2CO_2K or CH_2CO_2M where M is defined as above, and R^{13} is preferably $(CH_2)_2CH_3$ or



pale brown oil I.r.ν1754S C=O cm^{-1}.

Example 159, Compound 159:

Compound 158 from Example 158 was treated with ethanolic potassium hydroxide following the procedure in Example 36 to give the title product as a very pale orange solid.

Example 160, Compound 160:

Compound 159 was treated with HCl following the method of Example 38 to give the title product as a grey solid.

Example 161, Compound 161:

Compound 155 prepared in Example 155 was treated with concentrated sulphuric acid/nitric acid following the method in Example 13 to give the title product as a red solid I.r. ν 1730 S C=O cm^{-1}.

Example 162, Compound 162:

Compound 161 from Example 161 was treated with ethanolic potassium hydroxide following the method of Example 40 to give the title product as a pale yellow-brown solid. I.r. ν 1610 S C=O cm^{-1}.

PYROGALLOL-ALDEHYDE CYCLIC TETRAMERS AND DERIVATIVES

Example 163, Compound 163:

The title compound was prepared as a pale pink solid by the reaction of n-butyraldehyde and pyrogallol in 1:4, 37% aqueous HCl to ethanol under nitrogen under reflux for 90 minutes following the method of J. Holmes and P. Tasker, European Patent Application EP 400,773 5th December 1990 assigned to ICI.

Example 164, Compound 164:

The cyclic tetramer of pyrogallol and butyraldehyde prepared in Example 163 was treated with 4 equivalents of bromine in chloroform following the

method of Example 3 to give a pale grey-brown solid as the title compound after removal of all volatiles.

Example 165, Compound 165:

Compound 163 from Example 163 was etherfied with 24 equivalents ethyl bromoacetate and 18 equivalents $K_2 CO_3$ in refluxing dry acetone for 48 hours following the method of Example 14 to give the title product as a pale yellow oil.

Example 166, Compound 166:

Compound 164 from Example 164 was etherified as in Example 165 to give the title product quantitatively as a pale orange heavy oil. I.r. ν 1753S, 1740 sh C=Ocm^{-1}.

Example 167, Compound 167:

Compound 165 prepared in Example 165 was treated with ethanolic potassium hydroxide following the method of Example 36 to give off white title product, which was soluble in water, as were all acid salts which follow.

Example 168, Compound 168:

Compound 167 prepared in Example 167 was treated with HCl then washed with water following the method of Example 38 to give the title product as an off-white solid which was not very water soluble nor were all subsequent acid derivatives.

Example 169, Compound 169:

Compound 166 prepared in Example 166 was refluxed with 1g (0.018 mole) potassium hydroxide in 10 ml refluxing absolute ethanol for 2 hours. After this time a pale brown suspension of solid had formed in the reaction mixture which was filtered off under nitrogen (the solid appears to rapidly pick up moisture from the air and turns to a blackish oil).

The pale brown solid was filtered off, then washed with ethanol again under nitrogen, then dried in a round bottom flask purged with nitrogen. A

pale brown solid product was obtained which was stored in a sealed container. Yield = 0.8g = 83%. The product was very soluble in water.

Example 170, Compound 170:

Compound 169 prepared in Example 169 was treated with 37% HCl then water was added and the entire was cooled to $0^{o}C$ at which point it was filtered to give a brown solid which was air dried overnight to give 0.35g (92% yield) title product as brown solid stable in air which had very limited water solubility.

Example 171, Compound 171:

Compound 170 from Example 170 was treated with excess Analar 25% aqueous NH_4OH which instantly dissolved the product and then was left overnight in a $50^{o}C$ oven to give quantitative conversion to a pale brown solid title ammonium salt product.

This compound was tested i.v. in mice with no toxic effect at 200 mg per kg body weight.

Example 172, Compound 172:

2.6g (0.025 mole) 3-(methylthio) propionaldehyde from Aldrich was stirred under nitrogen under reflux with 3.15g (0.025 mole) pyrogallol in 40 ml ethanol and 10 ml 37% aqueous HCl for 90 minutes following the method in Example 163 to give 3.8g purple product 72% yield ??? Compound 172a which was washed with a minimum amount of cold $0^{o}C$ ethanol, then allowed to air dry overnight. It was quantitatively converted to Compound 172b by treatment with 4 equivalents of bromine in chloroform overnight (all volatiles subsequently removed under vacuum). This dark purple product was etherified quantitively with ethyl bromacetate following the method of Example 165 to give its ethyl acetate derivative as a pale brown heavy oil which was treated with an equal quantity of potassium hydroxide in ethanol as in Example 169 to give the title product as a yellow solid which was dried under nitrogen and stored in a sealed container.

Example 173, Compound 173:

Compound 172 from Example 172 was treated with HCl as in Example 170 to give virtual quantitive conversion to solid pale brown title product.

Example 174, Compound 174:

Compound 173 from Example 173 was treated with NH_4OH following the method in Example 171 to give quantitatively ammonium salt title product as an off-white solid.

Example 175, Compound 175:

The title compound was prepared as an off-white solid following synthesis of the tetramer from dodecanal and pyrogallol which was obtained as a brown solid and subsequent bromination, etherification with ethyl bromoacetate and hydrolysis with ethanolic potassium hydroxide as in Examples 163, 164, 166, and 169.

Example 176, Compound 176:

Compound 175 from Example 175 was treated with HCl following the method in Example 170 to give the title product as dark brown solid.

Example 177, Compound 177:

Compound 176 from Example 176 was treated with NH_4 OH following the method in Example 171 to give the title product as a red-brown solid.

Example 178, Compound 178:

The title compound was prepared as an off white solid following synthesis of the tetramer from pyrogallol and phenylacetaldehyde and conversion steps in Examples 163, 164, 166, and 169.

Example 179, Compound 179:

The title compound was prepared as a pale brown solid by treatment of its potassium salt from Example 178 with HCl following the method of Example 170.

Example 180, Compound 180:

The title compound was prepared as a pale yellow solid by treatment of the acid derivative from Example 179 with NH_4OH following the method Example 171.

Example 181, Compound 181:

The title compound was prepared as an off-white solid following synthesis of the tetramer from pyrogallol and m-bromobenzaldehyde and conversion steps in Examples 163, 164,166, and 169.

Example 182, Compound 182:

The title compound was prepared as a brown solid by treatment of its potassium salt from Example 181 with HCl following the method of Example 170.

Example 183, Compound 183:

The title compound was prepared as a pale brown solid by treatment of the acid derivative from Example 182 with NH_4OH following the method of Example 171.

Example 184, Compound 184:

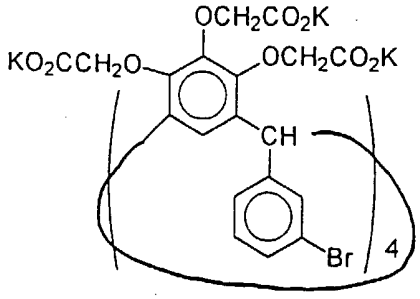
The title compound was prepared by ommitting the bromination step in Example 181, before the etherfication step and was obtained as a pale pink solid.

Example 185, Compound 185:

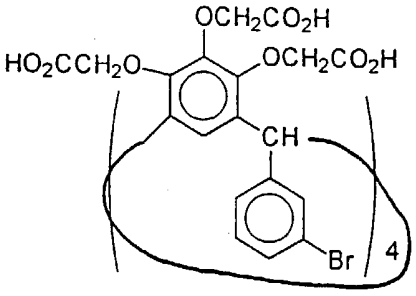
The title compound was prepared as an off-white solid by treatment of its potassium salt of Example 184 with HCl following the method in Example 170.

Example 186, Compound 186:

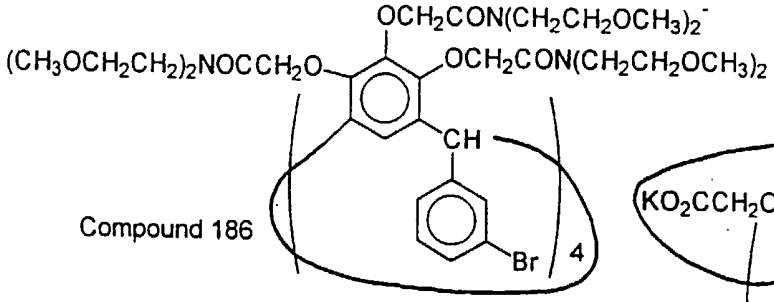
The title compound was prepared by treatment of the acid derivative in Example 185 with thionyl chloride then bis-methoxyethyl amine following the method in Example 132 and was obtained as a pale pink solid.



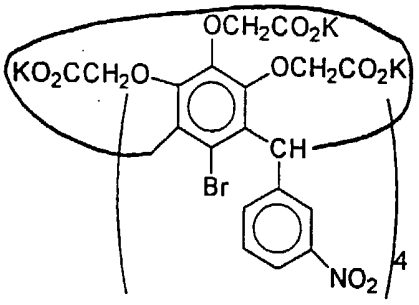
Compound 184



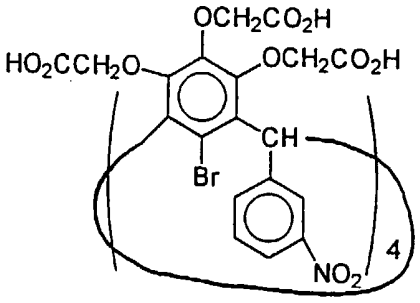
Compound 185



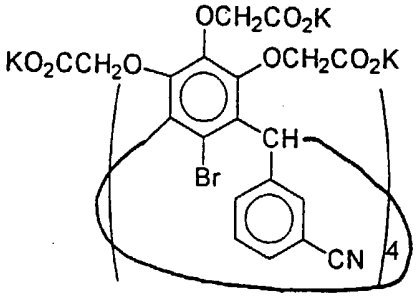
Compound 186



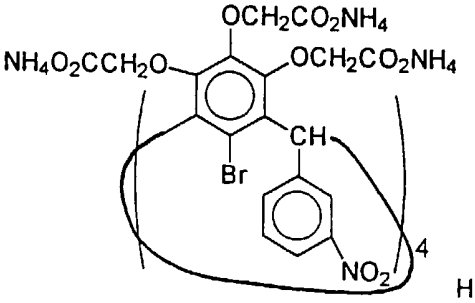
Compound 187



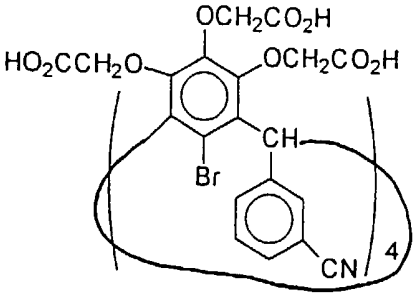
Compound 188



Compound 190



Compound 189



Compound 191